

To illustrate the points in my last email message, the following observations are needed.

1. A function, $f(x)$, is said to be differentiable at a point x_0 if its [HYPERLINK "<http://mathworld.wolfram.com/Derivative.html>"] (i.e., slope) exists at that point. The derivative for a function $f(x)$ at point x_0 is said to exist if $\lim_{x \rightarrow x_0^-} f(x) = \lim_{x \rightarrow x_0^+} f(x)$. That means the limits from left must equal to the limit from right at x_0 . Note that a function can be continuous but not differential at some point. The formaldehyde data seem to support (at least casting a doubt) that the slope at the bending point does not exist because it is not differentiable at this crucial point.
2. Since there is no such thing as a limit from left (this would imply a negative doses) at dose=0, slope of a dose-response function is not well-defined. Therefore, it is not meaningful to talk about a slope at dose=0 (mathematically, 0 is called the boundary point of the domain). This is why some theoretical articles have been written discussing about some statistical issues concerning the estimated parameters.
3. The B-Up approach avoids the problem in #2 above by allowing background doses to range from 0 to C_0 as shown in Fig 1 in Starr et al (2003, Regulatory Toxicology and Pharmacology). Note that in Fig 1, Starr essentially assumes a smooth (differentiable) dose-response function with the lower portion of the curve associated with the background doses. This is essentially identical to the background additive concept without having to cite the so-called "background additivity". This is why I wondered what Crump had in mind when he says that B-Up approach violates additivity assumption. I don't see anything wrong with Fig 1 as long as indigenous and exogenous adducts have the same biological effect.